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CASE REPORT

Case Report of Argininemia: The Utility of the Arginine/Ornithine Ratio for Newborn Screening (NBS)

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Abstract We describe a case of Argininemia detected by Michigan Newborn Screening (NBS). The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children recommends that every MS/MS newborn screening program include Argininemia as part of their uniform screening panel. While affected infants will be detected by this testing, Arginine levels may take time to accumulate. Thus, some infants may not be detected by this methodology and early sample collection. In Michigan, since initiating testing for Argininemia in 2006, there has been workup of 23 cases for elevated Arginine identified by NBS, with one case identified as affected. We report this affected case. Subsequently, the Arginine/Ornithine ratio was calculated for all cases and was found to be informative with respect to predicting whether a patient is affected by Argininemia.

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Introduction

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children recommends Arginemia be included in the NBS uniform panel (http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/ accessed September 11, 2012). Hyperarginemia (OMIM 207800) has an estimated incidence of one in 2 million births (Scaglia and Lee 2006). Arginase is the enzyme involved in the last step of the urea cycle and converts L-arginine into L-ornithine and urea. The Arginase A1 gene is located at 6 q23. Arginemia is an autosomal recessive disorder. As opposed to other urea cycle defects, review of the literature suggests that this condition does not classically present in the newborn period with symptoms of hyperammonemia. Onset is typically between 2 and 4 years of age. (Crombez and Cederbaum 2005)

One review of 55 patients with hyperarginemia indicated that 52 of the patients were asymptomatic in early infancy (De Dyn et al. 1997). If untreated however, these individuals go on to develop symptoms of psychomotor deterioration, loss of developmental milestones, and spasticity. With appropriate adherence to dietary and medication treatment, these symptoms may be prevented.

In some individuals it may take time for Arginine to accumulate in the plasma, which may be in part due to the presence of mitochondrial Arginase(Arginase II) which can increase up to 40-fold if cystosolic Arginase I activity in liver is deficient. There have been reports based on siblings of known Argininemia patients that the Arginine level can

be normal in the neonatal period in patients who will ultimately be affected. Conversely, unaffected patients in the newborn period may have Arginine levels above 150 umol/L and have normal Arginase activity.

Biochemical abnormalities include accumulation of Arginine which is the hallmark of hyperargininemia. Arginine can be measured by tandem mass spectrometry. From a survey among participants of a LISTSERV for metabolic specialists, while a number of cases have been detected, at least one has been missed (Crombez and Cederbaum 2005). Regarding this missed case in California, at that time the Arginine cutoff level was 200 umol/L, and the infant's Arginine level was under this level. The cutoff has since been reduced to 50 umol/L and this patient would have been identified (Cederbaum, June 21, 2012, personal correspondence). However, lowering the cutoff may contribute to more false positives being identified.

It would be helpful to have a test which could reduce false positive results in screening for hyperargininemia, and thus conserve resources by identifying which patients have clinical elevations in Arginine. Such a test was suggested by Currier: December 2010 Regional Collaborative Update. Specifically a new ratio, Arg/Orn, was recommended (Rinaldo 2010). This ratio was calculated for our Argininemia case, the previous elevated False Positive cases, and the normal population during the period of time since Michigan has instituted MS/MS Newborn screening.

Case Report

We present a case of an infant with an elevated Arginine of 107 μmol/L (nml <68 μmol/L) with newborn screening of dried bloodspot collection at 25 h. The Arginine/Ornithine ratio was calculated to be 2.47 (Table 1). The infant was born at 39 weeks to a G2P2 mother. Family history was unremarkable for any consanguinity, and the patient was of Dutch and Irish ancestry. Birth weight was 8 pounds and birth length was 20.5 in. The postnatal course was uncomplicated and the infant was discharged at 3 days of age. The infant subsequently did well, feeding and growing appropriately. However, a repeat NBS Arginine at day 19 of life was 499 μmol/L (nml < 110 μmol/L) which prompted further evaluation at the Children's Hospital of Michigan. In the ED, the ammonia level was initially 107μmol/L but on repeat was 49 μmol/L. The patient's plasma amino acids showed an elevated Arginine level of 762 μmol /L (nml 40–148). The patient was subsequently started on a protein-restricted diet of 2.2 g/kg which included Cyclinex metabolic formula. The family was counseled regarding Arginase deficiency, and given an emergency management protocol outlining medical management in the event the patient had symptoms of illness. Diagnosis was later confirmed by DNA analysis which showed two mutations in the Arginase gene; c.807–811 deletion (inherited from the father), c.611A > G (p. D204G) (inherited from the mother). Both of these are novel mutations and are predicted to be deleterious, causing the disorder.

Table 1 Arginine results with calculated Arginine/Ornithine ratio for patients identified as having elevated Arginine level by Michigan newborn screening <180 h of age. Case report patient highlighted.

Age (hours)	Arg (μmol/L)	Orn (μmol/L)	Arg/Orn
25	107	43	2.47
36	68	94	0.72
0	75	106	0.71
6	83	120	0.69
26	77	121	0.64
24	76	123	0.62
34	75	125	0.60
26	75	144	0.52
27	76	164	0.46
25	71	187	0.38
25	70	192	0.37
24	71	193	0.37
168	74	219	0.34
36	79	279	0.28

Results and Discussion

This was the first Argininemia case identified by the Michigan NBS Program since initiating testing for Arginine in 2006 (>675,000 samples tested). Twenty-three cases with elevated Arginine (not due to TPN feeding) had been identified. For these 23 cases, 22 had confirmatory testing accomplished by a repeat Arginine level, which were all within normal limits. Our case highlights the challenge of identifying a patient with Argininemia, and how best to confirm clinical suspicion of a patient with an elevated Arginine value.

The December 2010 Regional Collaborative Update presented a new ratio: Arginine/Ornithine proposed by Bob Currier (Rinaldo 2010). This prompted the MI NBS laboratory to calculate the Arg/Orn ratio for this Argininemia case, the previous presumptive positive cases, and the normal population.

The initial Arginine/Ornithine ratio was 2.47 for our case as measured at 25 h of age (Table 1). For the period 2006–2012, for patients not on TPN or hospitalized in the NICU, the mean Arginine value was 11.8, median value was 10.6 (SD = 6.12, 99 % = 31.90). The mean Arginine/Ornithine ratio for this time period was 0.14, the median

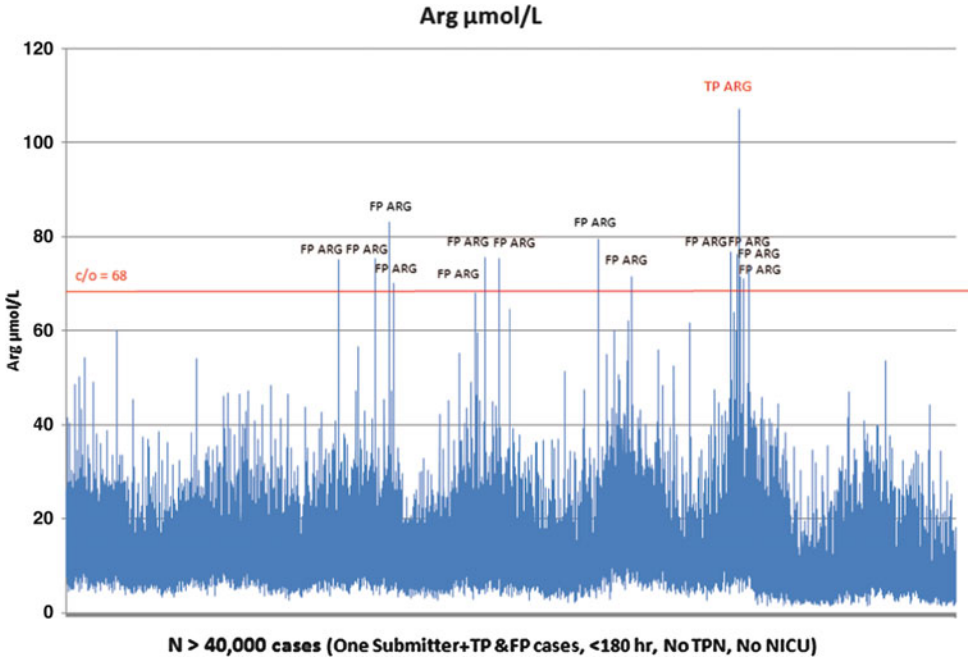

Fig. 1 Arginine Levels (umol/L) for newborn screening cases from one hospital in Michigan from 2006 to 2012 plus the MI false-positive cases and this Argininemia case. Arginine cutoff (c/o) = 68. FP = False positives, TP =True positives

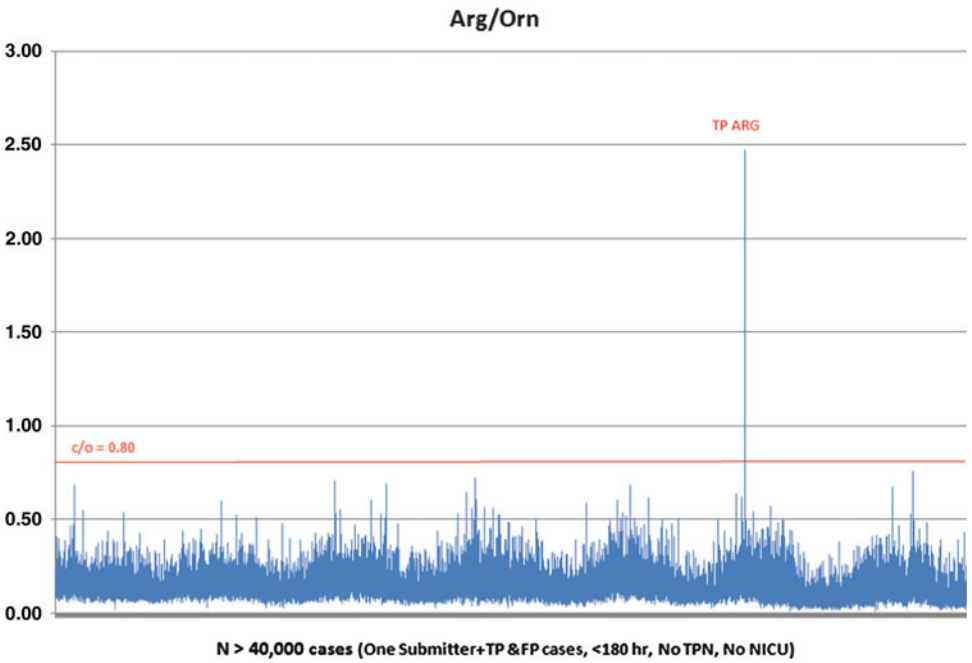

Fig. 2 Arginine/Ornithine ratios for newborn screening cases from one hospital in Michigan from 2006 to 2012 plus the MI false-positive cases and this Argininemia case, c/o = 0.80. TP = True positive

was 0.12 (SD 0.07, 99 % = 0.35). At present, the Michigan NBS Program has set the cutoff for Arginine/Ornithine ratio at 0.8 and is in the process of validating this ratio. To further illustrate the utility of this ratio, Fig. 1 represents the Arginine values for over 40,000 infants from one hospital in Michigan, plus the false-positive cases and this Argininemia case. For a number of infants, Arginine values were above the designated cutoff. Figure 2 represents the Arginine/Ornithine ratios for over 40,000 infants from one hospital in Michigan, plus the false positive cases and this Argininemia case. Only the infant that was a true-positive case for Argininemia had an Arg/Orn above 0.8.

This emphasizes the utility of the Arg/Orn ratio when screening for Argininemia patients.

Utilizing this ratio should both reduce the false positive rate for Argininemia and allow the Arginine cutoff to be lowered. It can serve as a tool to improve selectivity and sensitivity for detecting patients with this condition. In addition, if this ratio is not available to the clinician, this case illustrates the importance of repeat testing in the event of an elevated Arginine value above the cutoff. Plasma Arginine may be on an upward trend, as was the case with our patient.

Take-Home Message

The Arginine/Ornithine ratio may be an important tool in predicting which patients are affected by Argininemia.

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